PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Patent Application of Norman Orentreich, *et al.*	: Group Art Unit 1653
Conf. No.:	7858	:
Appln. No.:	09/309,689	: Examiner: A. Mohamed
Filed:	May 11, 1999	:
For:	MATERIALS FOR SOFT TISSUE AUGMENTATION AND METHODS OF MAKING AND USING SAME	: Attorney Docket No. **4555-45US**

DECLARATION OF ROZLYN KRAJCIK UNDER 37 C.F.R. § 1.132

I, Rozlyn Krajcik, declare and state as follows:

1. I am a co-inventor of the invention described and claimed in the above-identified patent application.

2. I am the Director of Scientific Affairs at the Orentreich Foundation for the Advancement of Science, Inc. ("OFAS"), the assignee of the above-identified patent application. I have held this position since 1994. I hold a Ph.D. from Wright State University.

3. I am and have been engaged in the development of soft tissue augmentation products at OFAS.

4. By virtue of my educational background, training and experience, I am at least one of skill in the art, as such term is used within the meaning of the patent statutes.

5. I am familiar with the prosecution of this patent application and, in particular, with the Office Action mailed January 9, 2003 (Paper No. 15), which I have reviewed. I have also reviewed each of the prior art references cited in that Office Action.

6. I am aware that claims 1-22 have been cancelled by the Amendment in support of which this Declaration is offered and new claims 23- 42 have been added. I have reviewed claims 22-42.

The Examiner's Position and the Purpose of the Declaration

7. In Paper No. 15, the Examiner has maintained the rejections of claims 1, 5-6, 8, and 22 of this application as anticipated by Coleman *et al.*, eds., Skin Resurfacing, pp. 217-234, 1998 ("Coleman"), and by Pollack, J. Dermatol. Surg. Oncol., Vol. 16, No. 10, pp. 957-961, October 1991 ("Pollack"), each taken individually. Office Action (Paper No. 15) (hereinafter "OA") at 3-4.

8. As basis for this rejection, I understand that the Examiner alleges that each of Coleman and Pollack teaches an injectable material for soft tissue augmentation which comprises cross-linked, blood plasma proteins that are purified and stabilized. In particular, the Examiner cites page 222, under the heading "FIBREL," of Coleman, and page 960, under the heading of "FIBREL," of Pollack. The Examiner argues that the FIBREL composition inherently contains cross-linked blood plasma proteins, merely because Coleman and Pollack teach that one may combine blood plasma into the FIBREL composition. *Id.*

9. I also note that in Paper No. 15, the Examiner has maintained the rejection of claims 1-22, arguing that they are obvious over Coleman or Pollack, each taken individually, in view of Grabarek *et al.*, Anal. Bichem., Vol. 185, pp. 131-135, 1990 ("Grabarek"); Wong, *Chemistry of Protein Conjugation and Cross-Linking*, pp. 39-40 and 195-207, 1991 ("Wong"); or Wang, *et al., J. Paren. Drug Assoc.*, vol. 34, No. 6, pp. 452-462, Nov.-Dec. 1980 ("Wang"). OA at 5-9.

10. The Examiner reasons that Coleman and/or Pollack describe cross-linked blood plasma proteins. Grabarek, Wang and Wong each describe cross-linking agents, zero-length cross-linking procedures, and amide-bond cross links that are between lysine-glutamate residues or lysine-aspartate residues as well as excipients and additives for parenteral formulations. *Id.*

11. In this Declaration, I provide evidence to show that the neither Coleman nor Pollack teaches a composition containing the cross-linked blood plasmas proteins of the

invention. Additionally, I proffer evidence that the combination of Coleman/Pollack and Grabarek, Wong and Wang does not render the material or the methods of the invention obvious, as (i) the combination does not teach cross-liked blood plasma proteins where the cross linkage is an amide bond, and (ii) a person of skill would not have made the combination nor had a reasonable expectation that the combination would be a successful composition or method for use as soft tissue augmentation materials.

Background and Purpose of the Invention

12. The invention is a material for soft tissue augmentation that can be used to aesthetically correct scars, wrinkles, or other similar depressed, dermal defects. The injectable material of the invention includes cross-linked blood plasma proteins having at least one amide bond. Within the scope of the invention is also contemplated a method of preparing the material and a method of soft tissue augmentation in which the material is used.

13. The injectable materials described in this patent application meet the need in the art for a safe, non-antigenic, non-irritating, longer lasting, and aesthetically pleasing injectable material for soft tissue augmentation that is relatively easy to obtain and to manufacture. The injectable materials of the invention are easily injected and, once injected, are more resistant to degradation by natural proteases than injectable materials known in the art. These properties are advantageous, because the environment in which the augmentation is most often to be used, intradermal compartments of human skin, is heavily populated with proteases, as well as components of the immune system.

Discussion and Analysis of the Prior Art Disclosing FIBREL®

14. Pollack and Coleman each provide disclosures pertaining to a product sold under the trade name FIBREL for use in the treatment of scars or wrinkles.

The Pollack Reference

15. Pollack teaches that the FIBREL product is "individually reconstituted for each patient treatment session." Pollack at 960, col. 1, lines 30-31. A small amount of the patient's

plasma is added to FIBREL, a mixture of (1) highly purified, denatured porcine collagen (gelatin) and (2) epsilon-aminocaproic acid. *Id.* at lines 32-34.

16. Pollack teaches that, once injected, the gelatin of the FIBREL composition acts as temporary matrix upon which the blood plasma constituents, such as fibrin, are deposited. *Id.* at col. 1, ll. 34-36. Pollack teaches that the episilon-aminocaproic acid is present in FIBREL to inhibit the "digestion" of fibrin, by inhibiting the production of fibrolysin. *Id.* at col. 1, ll. 36-38.

17. The Pollack reference also teaches that the "mode of action" of FIBREL involves the activation of the patient's own fibroblasts and subsequent collagen deposition by those cells, *i.e.*, deposition of host collagen, which production and/or deposition at the target augmentation site is induced by the FIBREL injection. *Id.* at col. 1, ll. 28-32.

18. Notably Pollack does not teach or suggest that any of the components of the blood plasma added to the FIBREL composition are cross-linked or even associated with one another in any manner. Nor does Pollack suggest that the cross-linking of the blood plasma proteins incidentally present in the blood plasma used to reconstitute the FIBREL is either desirable or necessary. To the contrary, Pollack makes clear that it is not the blood plasma proteins that are acting to augment the targeted tissue, but rather that it is the subsequently-deposited collagen, which is provided by the patient's own cells. *See id.*

The Coleman Reference

19. Similarly, the Coleman reference teaches that FIBREL contains porcine gelatin powder, Σ-aminocaproic acid, and can be mixed with the patient's own plasma. Coleman at col. 1, ll. 28-32. Coleman teaches that FIBREL was designed to stimulate collagen production by the patient's own cells at the site of injection. *Id.* at col. 1, ll. 22-23. It is also disclosed in Coleman that use of the composition without the addition of the patient's blood plasma is as effective as use of the composition that does contain the blood plasma, and is additionally advantageous, for it avoids any chance of inadvertent contamination of the physician or assistant with the blood plasma mixture during mixing. *Id.* at col.1, ll. 37-41.

FIBREL®- Physician Package Insert

20. As at least of person of skill in the art, I am familiar with the product of the gelatin matrix implant product distributed under the trade name FIBREL by Serono Laboratories, Inc., which is described in the Coleman and in the Pollack article. A copy of the Physician Package Insert ("the Package Insert") that accompanies the FIBREL product is attached hereto as Exhibit A.

21. The Package Insert describes FIBREL as a "device composed of absorbable gelatin powder (denatured types I and III) and episilon-aminocaproic acid ("EACA") in a lyophilized form." Exh. A at col. 1, ¶ 1. The Package Insert states that FIBREL may be reconstituted prior to use with equal parts of a sodium chloride solution and the patient's blood plasma. *Id.*

22. The Package Insert teaches that the blood plasma for use in the reconstitution of FIBREL is obtained by (1) drawing of whole blood into a collection tube containing anti-coagulant citrate dextrose and (2) the centrifugation of this whole blood, to separate out the blood plasma. The blood plasma is subsequently diluted with a sodium chloride solution. Exh. A at col. 3, ¶ 6.

23. The FIBREL product insert discloses the "mode of action" of FIBREL as follows:

> The reconstituted FIBREL® suspension forms a network with a gelatin matrix which initially restores the skin contour. EACA is an antifibrinolytic agent which inhibits the liquification of fibrin. Over a period of months the implant is colonized by the patient's own connective tissue cells and is subject to the same stresses and aging of normal host tissue.

Exh. A at col. 1, ¶ 3 (emphasis added).

Thus, according to the Package Insert, FIBREL serves to accomplish tissue augmentation by recruiting the patient's own cells to produce collagen at the target site.

The FIBREL Composition Does Not Contain Amide Cross-Linked Blood Plasma Proteins as Recited in the Claims

24. It is my understanding that in order for a prior art reference to anticipate a claim, the reference must describe all elements in the claim, either expressly or inherently.

25. It is my understanding that under the U.S. patent law a claim element cannot be found to be "inherently" present in a cited reference unless the Examiner has provided a basis in fact and technical reasoning to support the inherency determination.

26. Based upon the disclosure provided by Coleman or Pollack, a person of skill in the art would have known that reconstituted FIBREL does not contain cross- linked blood plasma proteins that include intermolecular cross-linkages that are amide bonds. No such cross linkages are described expressly or inherently in the references.

27. First, there is no express disclosure in either Coleman or Pollack that the blood plasma to be used for reconstitution of FIBREL is treated in any way so as to induce the formation of intermolecular cross-linkages that include amide bond(s). The references merely state that the blood plasma is mixed with the FIBREL powder to reconstitute it. Coleman at col. 1, ll. 28-32; Pollack at col. 1, ll. 31-34.

28. Nor is there any factual or technical basis that would have caused a person of skill to believe that either Pollack, Coleman and/or the Package Insert inherently described a tissue augmentation device having amide cross-linked blood proteins. Neither reference discusses or even alludes to any process by which such cross links could be formed in the FIBREL/blood plasma mixture.

29. The Package Insert serves as confirmation that the blood plasma is not treated or otherwise subjected to any processes that would result in the formation of amide bond cross-linkages of the constituent blood plasma proteins. To the contrary, the Package Insert discloses only that anti-coagulant citrate dextrose is added to the blood sample, prior to centrifugation to prevent blood coagulation (formation of blood clots by, *inter alia*, the conversion of the soluble blood plasma protein fibrinogen to the insoluble fibrin). Blood clotting, as is known to one of skill in the art, does involve formation of intermolecular bonds between/among certain types of blood plasma proteins.

30. Moreover, Pollack presents the hypothesis that the mode of action of FIBREL involves the deposition of fibrin on the collagen (gelatin) matrix formed at the injection site. As is known to a person of skill in the art, however, collagen is not a blood plasma protein,[1] and any attachment formed between the collagen matrix and, for example, fibrin, is a non-covalent hydrophobic bond, not an amide bond.

31. As is known to a person of skill in the art, intermolecular cross linkages that are amide bonds are not spontaneously and casually formed between and among blood plasma proteins present in fresh, untreated plasma, in the absence of human manipulation using reagents that promote and facilitate this bond formation.

32. In untreated plasma, such as that used to reconstitute FIBREL, there may very infrequently be transient intermolecular bonds formed between plasma proteins. These bonds are buffered by glutathione and other redox molecules also found in the bloodstream. Exh. B (6). These bonds are disulfide bonds, not amide bonds. *Id.*

33. The formation of these transient inter-molecular disulfide bonds is very rare, and is highly regulated by the enzyme systems of the blood. Indiscriminate, casual formation of even the less stable disulfide bonds between/among blood plasma proteins would lead to formation of thrombosis and subsequent death of the organism. Exh. B.

34. The data presented in the application itself also supports the conclusion that no amide bonds are formed in untreated plasma (such as is used in the reconstitution of the FIBREL composition). Comparative Example 1 describes the preparation of a material that was made using untreated blood plasma. Specification at 18. The blood plasma was collected, and treated only with EDTA, an anticoagulant that acts similarly to the EACA used in the FIBREL composition. *Id.* Vitamin C was also added to the plasma. No further treatment was applied.

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[1] Blood plasma proteins include serum albumin proteins, very low density lipoproteins (VLDLs), low density lipoproteins (LDLs), high density lipoproteins (HDLs), immunoglobulins, fibrinogen (the soluble precursor protein to fibrin), prothrombin, transferrin, and other transport proteins. Specification at page 8. Collagen is any one of a group of proteins that forms connective tissues in mammals. It is not present in blood plasma.

35. The composition of Comparative Example 1 was injected into hairless mice. Spec. at 19 (Comparative Use Example 1).

36. The results of Comparative Use Example 1, compared to the results obtained using the tissue augmentation device of the invention, are shown in Table 1. Spec. at 21-22.

37. Table 1 shows that 418 days after injection to the augmentation site, the augment volume of the Comparative Use Example 1 (plasma alone) was approximately 25% of its initial volume. In contrast, the augmented volume of Use Example 1 shows that after 693 days, the volume has only lessened by a mere 25% of its original volume, and maintained 75% of its volume.

38. These data demonstrate that the bonds formed between/among the blood proteins of the composition are not the same as the bonds (if any are formed at all) that may exist between/among the blood proteins of the untreated plasma that is mixed with the FIBREL composition.

39. For at least these reasons, there is no technical or scientific basis supporting the assertion that FIBREL reconstituted with blood plasma "inherently" contains blood plasma proteins that are intermolecularly cross-linked and contain at least one amide bond.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that those statements were made with the knowledge that willful false statements the like so made are punishable by fine or imprisonment, or both, under Section 1003 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

7-1-03 (Date) By: Rozlyn Krajcik
ROZLYN KRAJCIK